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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,621	11/21/2003	Luis H. Toledo	TOL01 P-100A	3490

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EXAMINER
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ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,621	TOLEDO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending in this application.

Election/Restrictions

Applicant's election of Group I (i.e., claims 1-10, 13-16 (in part) and 17-18 drawn to compounds of formula (II), corresponding method of use) in the reply filed on March 14, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11-12 and 13-16 (in part) (drawn to compounds of formula (IV) and corresponding method of use) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 14, 2006.

Note: In addition to the election of a single group, election of a species falling within the elected group was also required in the previous office action. Applicant did not provide with an election of a single disclosed species. However, upon reconsideration, the election of species requirement is withdrawn and the claims are searched and examined with the respect to the elected invention of Group I, drawn to compounds of formula (II).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating ischemic stroke, does not reasonably provide enablement for a method of treating for all of the ischemic diseases including coronary heart disease, hemorrhagic shock, peripheral vascular disease (upper and lower extremities) and transplant related injuries generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 13 is drawn to 'a method of treating a human who has an ischemic disease selected from coronary heart disease, peripheral vascular disease, etc. '. As can be seen from the definitions of the terms "ischemic disease", "coronary heart disease", "peripheral vascular disease", "transplant injuries", they include without limitation many types of diseases and therefore, the claims are seen to encompass methods of treating a wide variety of diseases. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a

format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

There are no testing assays provided in the specification related to the activity of the compounds and applicant did not state on record or provide any guidance regarding types of test assays to find the clinical efficacy of the compounds in the treatment of various disorders of the claims. As can be seen from specification pages 14-15, the dosage regimen is accurately determined 'by measuring the blood level or concentration of the nitroso compounds in the patient's blood and/or the patient's response to the particular condition being treated'.

The instant claims are drawn to "a method treating ischemic disease selected from coronary heart disease, stroke, hemorrhagic shock, peripheral vascular disease, and transplant related injuries". First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is therapeutic agents for the treatment of ischemic diseases, however, the specification does not provide any test assays or data regarding how the compounds correlate to the treatment of the various disorders of the instant claims. Some of the diseases and disorders encompassed by the instant claims have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area. It is inconceivable as to how the claimed compounds can treat all types of diseases of the instant claims generally. Further, there is no disclosure regarding how the patient in need of the treatment requiring treatment is identified and further, how all types of the diseases are treated. The state of the art reference, Zhang (Medline Abstract) indicates therapeutic benefits of NO donors during recovery from ischemic stroke.

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating' effect of a 'disease' solely based on the therapeutic activity stated for the compounds.

The terms 'ischemic diseases', 'coronary heart diseases' and 'peripheral vascular diseases' embrace a vast array of problems, many of which are contradictory to others. Thus, the terms cover hypertension and hypotension. Further, the terms include various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral

vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of thousands of compounds, could possibly be effective against such disorders generally.

The state of the art is not indicative of any nitroso therapeutic agents for treating ischemic diseases in general. The examiner notes, there is not seen sufficient guidance provided to the skilled artisan to practice the therapeutic methods, in the form of administration profiles, combination ratios of the active agents or references to same in the prior art. The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests to determine the efficacy of the compounds, that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The state of the art is not indicative of any therapeutic agents that are generally useful in the treatment of the claimed disorders and therefore, asserts the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an

insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, it is recited that "A piperazinyl pyrimidinyl nitroso compound.... **and** pharmaceutically acceptable salts thereof", which is unclear because it is not clear if 'a compound or a salt thereof' is claimed **or** 'a **mixture** of a compound and the salt' is claimed. Replacing with -- A piperazinyl pyrimidinyl nitroso compound..... ~~and~~ or a pharmaceutically acceptable ~~salts~~ salt thereof -- would overcome the rejection.
2. In claim 1, the definitions of the various variables are not recited in the alternative.

- See the definition of the term " (P)-R_N " wherein the last term 'C_1-C_6 alkyl' should be recited as -- or C_1-C_6 alkyl --.
- The definition of (P)-$R_{2\text{-}1}$ should be recited as -- -N=O ~~and~~ or C_1-C_6 alkyl; --.
- Following the recitation of 'wherein (P)-$R_{2\text{-}2}$ is C_1-C_6 alkyl;', the term "and" should be replaced with -- or --.
- In the definition of wherein (P)-$R_{2\text{-}1}$ and (P)-$R_{2\text{-}2}$ taken together, the last two terms should be separated by -- and -- (i.e., morpholinyl, and 4-nitroso-1-piperazinyl;).
- The definition of (P)-$R_{4\text{-}1}$ should be recited as -- -N=O ~~and~~ or C_1-C_6 alkyl; --.
- Following the recitation of 'wherein (P)-$R_{4\text{-}2}$ is C_1-C_6 alkyl;', the term "and" should be replaced with -- or --.
- In the definition of wherein (P)-$R_{4\text{-}1}$ and (P)-$R_{4\text{-}2}$ taken together, the last two terms should be separated by -- and -- (i.e., morpholinyl, and 4-nitroso-1-piperazinyl;).

3. Claim 18 does not end with a period.

Allowable Subject Matter

Claims 1-10 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action. The closest reference of record, U.S. Patent No. 5,380,724 does not teach or fairly suggest the instantly claimed compounds. The reference teaches 1-(tert-butoxycarbonyl)-4-(2,6-diamino-5-nitroso-4-pyrimidinyl)-piperazine compound, see col. 33, Example 59, compound b) as an intermediate compound. The instantly claimed compounds differ by having tertiary amines at the analogous positions. The reference does not teach or fairly suggest such compounds.

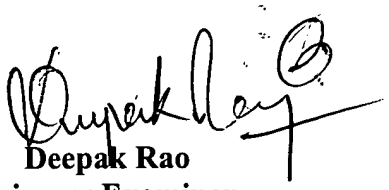
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

May 16, 2006